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AUTOIMMUNE ENCEPHALITIS WITH ANTI-NMDAR ANTIBODIES IN MULTIPLE MYELOMA – CASE REPORT AND LITERATURE REVIEW

AUTOIMMUNOLOGICZNE ZAPALENIE MÓZGU Z OBECNOŚCIĄ PRZECIWCIAŁ ANTY-NMDA W PRZEBIEGU SZPICZAKA MNOGIEGO – OPIS PRZYPADKU I PRZEGLĄD LITERATURY

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Abstract

Purpose: The initial presentation of autoimmune encephalitis (AIE) may resemble other disorders and a comprehensive investigation is required. In this paper we emphasize the challenges faced by a treating team performing a differential diagnosis and the necessity for insightful multidisciplinary collaboration.

Case description: We report on the case of a 67-year old man who developed transient disturbances of consciousness in the course of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, which was the first manifestation of malignant myeloma. To our knowledge, this is the first case of anti-NMDAR encephalitis associated with multiple myeloma described in the literature.

Comment: AIE with anti-NMDAR antibodies has become a well-characterised variant of the condition. AIE may or may not be associated with tumour; therefore it is necessary to use the screening approach for primary malignancy. A proper diagnosis is essential in management due to AIE's potential to respond to immunotherapy and tumour removal if one is present.

Key words: multiple myeloma, autoimmune encephalitis, anti-NMDAR antibodies, paraneoplastic neurological syndrome.

Streszczenie

Cel: Szerokie spektrum niespecyficznych objawów neuropsychiatrycznych prezentowanych przez osoby z autoimmunologicznym zapaleniem mózgu z obecnością przeciwciał anty-NMDAR dość często opóźnia rozpoznanie i implikuje konieczność przeprowadzenia interdyscyplinarnej diagnostyki różnicowej. Celem niniejszej pracy jest przedstawienie opisu przypadku chorego z anty-NMDAR autoimmunologicznym zapaleniem mózgu, ze szczególnym uwzględnieniem trudności diagnostycznych.

Opis przypadku: W pracy przedstawiono przypadek 67-letniego mężczyzny z anty-NMDAR autoimmunologicznym zapaleniem mózgu, u którego ostre zaburzenia świadomości były pierwszą manifestacją szpiczaka mnogiego. Dotychczas taki związek tych jednostek chorobowych nie był opisywany w dostępnych doniesieniach.

Komentarz: Autoimmunologiczne zapalenie mózgu z obecnością przeciwciał anty-NMDAR jest jednym z lepiej scharakteryzowanych typów autoimmunologicznych zapaleń mózgu o stopniowo rosnącej rozpoznawalności i korzystnym potencjale terapeutycznym. W niektórych przypadkach może towarzyszyć chorobie nowotworowej i wyprzedzać jej rozpoznanie, wówczas określane jest jako neurologiczny zespół paraneoplastyczny. W procesie diagnostycznym typ zidentyfikowanego przeciwciała może ukierunkować dobór badań przesiewowych w celu zlokalizowania pierwotnego procesu nowotworowego.

Słowa kluczowe: szpiczak mnogi, autoimmunologiczne zapalenie mózgu, przeciwciała anty-NMDAR, neurologiczny zespół paraneoplastyczny.

PURPOSE

Autoimmune encephalitis (AIE) comprises a spectrum of neurological disorders. It is seeing gradually increasing recognition and there is potential for it to respond well to treatment. Its clinical presentation, neuroimaging and laboratory results may mimic other disorders, which may result in a delayed diagnosis as well as late implementation of adequate treatment. In some cases AIE may be associated with malignancy, which is known as paraneoplastic autoimmune encephalitis (PAE). The clinical presentation of PAE is secondary to the autoimmune reaction triggered by the expression of specific onconeuronal antigens on neoplastic cells, which physiologically occur in the central nervous system [1]. Several classes of antibodies have been described in association with PAE. The recognition of PAE is based on neuroimaging, electroencephalography and cerebrospinal fluid tests, but their specificity and sensitivity are limited [2]. The indication of specific onconeuronal antibodies in serum or CSF is crucial in the course of diagnosis. The first group of intracellular onconeuronal antibodies typically appears to accompany the tumour. The second group of antibodies targeting surface-cell antigens like the anti-N-methyl-D-aspartate (anti-NMDAR) antibody are less often suspected to have a paraneoplastic aetiology. The anti-NMDAR encephalitis is one of the most comprehensively characterised types of AIE, but its wide range of neuropsychiatric symptoms often indicate the need for an interdisciplinary differential diagnosis. The aim of proper treatment is the removal of the source of the antigens via tumour removal and immunomodulatory therapy. The presence of the onconeuronal antibodies indicates the need for an extensive tumour search [1].

We report the case of a 67-year old man with PAE, who was admitted to hospital with rapidly increasing disturbances of consciousness. In the course of differential diagnosis the examination revealed anti-NMDAR antibodies in serum and the patient was diagnosed with multiple myeloma (MM). To the best of our knowledge, this is the first case of anti-NMDAR encephalitis associated with MM reported in the literature.

CASE REPORT

A 67-year old man, an academic worker with diabetes mellitus and no past psychiatric history, appeared at the emergency unit with acute onset of impaired consciousness which occurred after awakening. The symptoms were preceded by a 4-week course of fever and weight loss during which the patient was treated with empirical antibiotic therapy due to an upper respiratory tract infection.

On admission to the Department of Neurology, the patient was afebrile and haemodynamically stable. There were no other abnormalities found in the neurological examination aside from disorientation, delirium and speech disturbances (aphasia). The basic laboratory tests were within normal ranges. The brain computer tomography and chest X-ray did not reveal any pathologies. Analysis of the cerebrospinal fluid showed increased cytosis (144/3) and protein level (0.97 g/l) with a normal glucose level and negative serum inflammation markers. Due to the suspicion of encephalitis, empirical intravenous treatment with ceftriaxone and acyclovir was started during bacteriological testing of the CSF. Magnetic resonance imaging (MRI) displayed small, diffused areas of non-specific demyelisation without restriction of diffusion in the DWI/ADC map or any abnormalities, suggesting herpetic encephalitis.

On the fourth day of hospitalisation the consciousness disturbances retreated. The bacteriological tests of the CSF were negative. The follow-up CSF samples were taken on the eight day of hospitalisation (blood – iatrogenic). Lymphocytic cytosis (627/3) and elevated protein level (2.25 g/l) could still be observed.

The patient was screened for the source of the inflammation. Thyroid and abdominal cavity ultrasound examinations were conducted. The patient was given laryngological and dental examinations. An unclear change was observed in the panoramic radiograph, localised near the right temporomandibular joint. A CT of the jaw was made and the patient was seen by a maxillofacial surgeon. There were no obvious causes of inflammation.

In the differential diagnosis we took into account vasculitis and paraneoplastic syndrome. The follow-up brain MRI was similar to the previous one. The magnetic resonance angiography also did not reveal any abnormalities. In laboratory tests, Ca 15-3 antigen was slightly increased. The remaining common paraneoplastic markers and intracellular onconeuronal antigens were within normal ranges. The CSF check-up analysis of cytosis and protein levels taken after 2 and 3 weeks of hospitalisation showed a slight downward tendency (lymphocytic cytosis 265/3, 231/3; protein level 0.78 g/l, 0.85 g/l), but they were still comparable with the initial level. The intrathecal synthesis of immunoglobulin was identified. The cytology and follow-up bacteriological tests remained normal.

Due to the stable clinical presentation, which did not correlate with the CSF findings, AIE was suspected. Anti-NMDAR antibodies were identified in the patient's serum. Electroencephalography (EEG) showed diffused slow waves. The patient was screened for a tumour. Urological examination, gastroscopy and colonoscopy proved irrelevant. A thoraco-abdominal-pelvic CT scan suggested lytic metastasis in the skeletal system, which pointed out the paraneoplastic aetiology of AIE.

The PET-CT with fluorodeoxyglucose confirmed the lytic metastasis and showed extensive, destructive change in. The haematological disorder was taken into account in the differential diagnosis. Serum protein electrophoresis identified a monoclonal spike in the gamma glob-

ulin fraction with the total protein level within the normal range. Immunofixation detected IgG monoclonal protein with kappa light chain specificity in the serum, whereas it was absent in the urine. Histopathological examination of the sacral mass revealed plasmacytoma, which was confirmed by a bone marrow biopsy.

COMMENT

AIE is a relatively rare disease but is becoming increasingly better recognised due to the development of diagnostic techniques. Its heterogeneous clinical presentation may mimic other pathologies of the central nervous system, implying the need for insightful interdisciplinary investigation and therefore a possible delay in proper treatment [3-5].

AIE may be associated with underlying malignancy and, based on the diagnostic criteria of Graus *et al.*, can be retrospectively classified as either paraneoplastic or non-paraneoplastic syndrome [6]. The estimated incidence of neurological paraneoplastic syndromes (NPS) is about < 1%. However, more recent data shows that its frequency may be higher [3]. In 2016 new diagnostic criteria for autoimmune encephalities were proposed by Graus *et al.* [7].

The neuropsychiatric spectrum of clinical presentation of NPS is an effect of autoimmune mediated reaction triggered by the expression of onconeuronal antigens on neoplastic cells, which physiologically occurs in the CNS [1].

Tumours are usually associated with specific onconeuronal antigens, which calls for diagnostic and therapeutic management as well as prognosis. Based on the location of the antigens, AIE can be classified into two broad groups. Group I (anty-Hu, Yo, Ri, Ma/Ta, CV2, GAD, amphisin) targets intracellular antigens and shows a clear predilection to malignancy. The research has displayed its adverse response to immunomodulatory treatment and its poor outcome. Group II antibodies directed against cell-surface antigens (anty-NMDA, VGKC, VGCC, GABAr, AMPAr, GluR3) less frequently accompany malignancy and gives the appearance of better responding to treatment. However, the second group of antigens was also observed in patients with systemic diseases without underlying malignancy as well as after viral infection or vaccination [2, 3, 8, 9].

Anti-NMDAR encephalitis has become one of the most thoroughly described forms of AIE so far. The first report of anti-NMDAR encephalitis was published in 2005 and until now about 600 cases have been diagnosed [10, 11]. The actual incidence of this disease is unclear, but on the basis of an increasing amount of reports it is likely that it is more frequent than any other forms of the condition [12]. Additionally, epidemiological reports have found that its incidence exceeds the viral encephalitis [13]. One of the retrospective studies among patients in the 18-35 age range, hospitalized due to encephalitis with unknown origin, documented the anti-NMDAR antibodies in 1% cases [14]. In another multicentre prospective study this amount was estimated to be 4% and was found to be second most common after acute disseminated encephalomyelitis (ADEM) cases of AIE [12, 15]. Anti-NMDAR encephalitis mostly involves women (60%) and children (35%), while it affects men and elderly people less frequently [4].

Clinical and laboratory studies have shown that neuronal dysfunction results from blockage by IgG antibodies and increased internalisation of receptors of the extracellular epitope region located in the *N*-terminal domain of the NR1 subunit of the NMDA. This pathomechanism is reversible [2, 16-18]. The antibodies can be detected both in serum and CSF, though researchers have proved that CSF tests have better sensitivity and specificity [19]. The clinical effect of NMDAR antibodies is similar to the pharmacological impact of ketamine or phencyclidine, which are called dissociative anaesthetics [16]. The clinical symptoms correlate with the location of NMDAR in the hippocampus, the brain cortex and the amygdaloid nucleus.

On the basis of the criteria of Graus *et al.*, the disease can be classified as either "probable" or "definite" anti-NMDAR encephalitis [7].

The typical course of anti-NMDAR AIE is subacute and progressive, with fluctuations of the neuropsychological state [4]. The initial symptoms are nonspecific. In 50-70% of cases prodromal viral-like symptoms such as fever, nausea, diarrhoea and upper respiratory tract disorder occur and within days are followed by a wide range of psychiatric (behaviour disturbances, catatonia, delusions, psychosis) and neurological (cognitive impairment, language disintegration, seizures, oro-lingual dyskinesias, limb and trunk choreoathetosis, opisthotonic postures) manifestations, which may lead to disturbances of consciousness and a state of unresponsiveness. A problem with speaking, with its initial impoverishment, echolalia and echopraxia leading to mutism in its later stages, cannot be classified as cortical aphasia. Some patients develop central hypoventilation and autonomic instability (hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, erectile dysfunction) and need to be managed in intensive care units [2, 8, 9, 12, 20].

Evidence from the research shows that there are differences in the early phase of the disease between children and adults. The most of elderly patients present psychiatric disturbances in the initial presentation of anti-NMDAR encephalitis. Rarely, the psychosis, as well as abnormal movement or seizures, can be the isolated episodes that may result in a misdiagnosis and admission to psychiatric facilities [10, 21]. By contrast, children tend to present movement disturbances or seizures. In fewer than 4% of cases the course of the disease was mono-

symptomatic [2, 8, 9, 20]. A cohort study revealed that among patients older than 45 years anti-NMDAR AIE affects men more often than women, and that its course is milder, which causes a delay in recognition and treatment implementation [22].

The brain MRI in anti-NMDAR AIE can be either normal or may show nonspecific demyelination. In 65-80% cases T2 and FLAR signal hyperintensivity has been observed in the medial temporal lobes, the cerebellar or cerebral cortex, the basal ganglia and the brainstem, and in rare cases the spinal cord. These changes may present subtle contrast enhancement. The follow-up brain MRI may be normal or may reveal brain atrophy [2, 5, 8, 12, 23].

Recent studies carried out using positive emission tomography with fluorodeoxyglucose (FDG-PET) have identified some characteristic patterns for anti-NMDAR encephalitis. Hypermetabolism in the frontal and temporal lobes, in contrast to relative hypometabolism in the occipital lobes of the cerebral glucose metabolism, has been observed. What is more, the reports suggested a correlation between disease severity and a return to normality after recovery. Another piece of research based on single-photon emission computed tomography (SPECT) showed distinctive, multifocal cortical and subcortical changes of variable character during the course of the disease. In some cases these changes may be absent in the early stages [8, 12, 24].

Electroencephalography (EEG) in patients with anti-NMDAR encephalitis is estimated to be abnormal in more than 90% cases. Usually EEG shows diffused slow waves and disorganised activity with less common foci of the epileptic activity. Some patients present a pattern unique for anti-NMDAR encephalitis, referred to as extreme delta brush (EDB) due to the rhythmic activity of delta-theta waves with superimposed bursts of rhythmic beta frequency activity. Reports suggested that the characteristic pattern was associated with longer hospitalisation and a poorer outcome. It was observed especially among patients in coma and was not modified by antiepileptic drugs [2, 4, 12, 25].

The CSF examination reveals abnormalities in 80% patients in the early stages of the disease. Most AIE are associated with the presence of mild-to-moderate lymphocytic pleocytosis and an increased protein concentration level. Less frequently, oligoclonal bands are detected.

The identification of onconeuronal antibodies in serum or CSF is crucial in the diagnosis of AIE. Considering the limitations of a laboratory investigation, the results must be interpreted individually based on clinical presentation. Research shows that the sensitivity and specificity of CSF tests are better than the serum ones. It is important to distinguish between particular classes of immunoglobulin, especially IgG, IgM and IgA. The presence of antibodies in the IgG class of immunoglobulin is characteristic for anti-NMDAR encephalitis. IgM and IgA anti-NMDAR antibodies have been identified in patients with schizophrenia and also in 10% of cases of healthy individuals, whereas IgG anti-NMDAR antibodies were not detected [4, 8, 9].

The identification of the onconeuronal antibodies signals the need for an extensive tumour screening. The selection of diagnostic methods is made according to the class of antibodies detected and the patient's age and sex [5].

Anti-NMDAR encephalitis predominates in women in the 12-45 age range (53%) and in most cases ovarian teratoma has been identified (94%). A lower percentage of malignancy was detected among patients older than 45 years. In the second group, teratomas in other locations were more often observed as well as lung, breast, testis, thymus, pancreas and ovarian tumours. Men and children younger than 12 years old are affected in about 6% cases [2].

The case described here is the first reported in literature with anti-NMDAR encephalitis during the course of multiple myeloma. We found that two cases of stiff-person syndrome associated with presence of the anti-GAD antibodies in multiple myeloma have been described [26, 27].

Diagnosis of malignancy is relevant due to the following aspects:

1. Adequate tumour therapy allows treatment of autoimmune encephalitis.
2. Oncological and immunomodulatory treatments may demand a fixed scheme.
3. The implementation of treatment in AIE (corticosteroids, rituximab or cyclophosphamide) prior to the recognition of malignancy may delay the proper diagnosis and targeted treatment [8].

The European Federation of Neurological Sciences (EFNS) recommends a selection of screening tests on the basis of the onconeuronal antibodies detected and the sex of the patient. Due to the high probability of ovarian teratoma, transvaginal ultrasound is the investigation of first choice, followed by CT or MRI of the abdomen and/or pelvic region. In young women the CT examination should not be conducted due to the high doses of radiation. The screening tests for breast tumour are mammography and then MRI. The whole body FDG-PET is usually negative in a patient with ovarian teratoma, whereas it can be helpful in a case of thymoma or lung tumour with normal thorax CT. When a testicular tumour is suspected an ultrasound and then CT of the pelvic region should be made. According to the recommendations, patients with a negative primary screening should undergo screenings for tumour in 6-month periods for 2-4 years. The guidelines do not include any indications for lymphoma, small cell lung carcinoma or neuroblastoma due to the inadequate number of cases diagnosed, which do not for the formulation of recommendations [2, 28].

Anti-NMDAR encephalitis has a characteristic but nonspecific clinical picture; there is no pathognomic symptom,

which would result in a wide interdisciplinary diagnostic process.

Usually, within the first weeks of the disease the empirical antibiotic and/or antiviral therapy is implemented, as in our case. Here, bacteriological aetiology was ruled out due to the negative bacteriological tests of the blood samples and CSF. The PCR examination seeking to establish the presence of HSV in CSF proved the high sensitivity and specificity. However, it might remain false-negative within the first 24 hours of symptoms. An HSV aetiology was excluded on the basis of the normal results of the CSF/serum index for HSV, lack of changes typical for herpetic encephalitis in a double-checked brain MRI and persistent abnormal CSF results despite the treatment implemented. The HHV-6 viral infection can cause limbic encephalitis in immunocompromised patients. Our patient was immunocompetent, thus HHV-6 encephalitis was unlikely.

The reasons for the prodromal viral-like period in anti-NMDAR encephalitis remains unclear. One piece of clinical research revealed that a viral aetiology is unlikely due to the negative results of insightful CSF analysis, brain biopsy and tests for infection [18]. At the same time, a recently conducted study has shown that anti-NMDAR encephalitis appeared in patients who had suffered from herpetic encephalitis 2-6 weeks earlier [23].

In differential diagnosis acute disseminated encephalomyelitis (ADEM) should also be taken into consideration. It is characterised by diffused demyelinating foci in the central nervous system. In some cases it affects the optic nerves and the spinal cord. These symptoms were not observed in the reported case.

Vasculitis of the central nervous system may resemble AIE in some cases and confirming it in with neuroimaging shows the necessity of an exploration for systemic diseases.

Patients with systemic lupus erythematosus may also present an acute onset of neuropsychiatric symptoms. However, reports indicate that in most cases these symptoms coexist with an acute phase of a problem in another organ or systemic disease.

Encephalitis may be the first manifestation of CSN lymphoma or carcinomatous meningitis. Therefore the repetitive cytology of CSF and screening tests may help in proper diagnosis [2, 8].

Rapidly progressive neuropsychiatric disturbances suspected to be Creutzfeldt-Jacob disease (CJD) should also be distinguished from AIE. There have been reports suggesting the presence of anti-NMDAR antibodies in the serum of some patients with CJD. However, another multicentre study did not detect the presence of anti-NMDAR antibodies in CSF among patients with pathologically confirmed CJD. Additionally, in patients with anti-NMDAR encephalitis the 14-3-3 protein was not identified in the CSF [29].

The aim of proper treatment of NPS is the removal of the source of antigens by targeted ontological treatment and immunotherapy [1]. Corticosteroids, intravenous immunoglobulin and/or plasma exchange form the first line of immunotherapy. The second line of treatment is rituximab and/or cyclophosphamide. Clinical research among patients in the 1-85 age range revealed that immunotherapy combined with tumour resection was associated with a substantial neurological improvement in 81% of cases [11]. Furthermore, a better response to immunomodulating treatment was observed in patients with tumour resection and the second line therapy was less frequently implemented in comparison with patients without the associated malignancy [12].

Conflict of interest/Konflikt interesu

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